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(54) **Solid lipid microspheres having a narrow size distribution and method for producing them**
Feste Lipid-Mikrokugeln mit enger korngrosser Verteilung und Verfahren zu ihrer Herstellung
Microsphères lipidiques solides à distribution de dimension étroite et procédé pour leur production

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Description

Prior Art

Lipid microspheres consisting of oil drops in an aqueous dispersion were first investigated for parenteral nutrition and more recently also as vehicles of pharmaceutical substances (Shenking A. *World Rev. Nutr. Diet.* **28**, 1-111, 1978).

More recently systems based on soy oil emulsions, lecithin and suitable drug concentrations in water were developed for parenteral and oral administration (Mizushima Y. *Drugs Exptl. Res.*, XI (9), 595-600, 1985; Mizushima Y. et al., *J. Pharm. Pharmacol.*, **38**, 132, 1986; Ozona Y. et al., *Arzneim.-Forsch.* **36**, (I), 689-690; patents JP 61,249,918,7 Nov. 1986 and JP 61,263,914,21 Nov. 1986). Said systems do not have a well defined dimensional distribution of the oil drops nor stability with time.

Liquid emulsions were employed also by Hashida et al. for the lymphatic absorption of drugs (*J. Pharmacokin. Biopharm.* **3**, 241-255, 1977). The prepared systems were particularly unstable and it was necessary to administer them within a very short time from the preparation.

Other liquid lipid system were prepared for oral administration and lymphatic absorption of drugs, such as linoleic acid and surface active agent mixtures (Josphikawa H. et al: *Pharm. Res.* **5**, 249 (1985) or of bile salts and glycerylmonooleate (Joshihawa R. et al. *Int. J. Pharm.* **13**, 321 (1983) 9.

Finally, microemulsions of oils in water should be mentioned, such as for instance those based on particles microemulsified and encapsulated in a coacervation film using substances such as phospholipids, polymerizable lecithins, sphingomyelins (EP 274431). Solid lipid microspheres were, on the other hands, suggested by Stanislaw (Stanislaw J. Zdislaw J. *Acta Pharm. Technol.* **33** (3), 154, 1987). Such microspheres were prepared by mixing the active component with low melting materials, such as cetyl alcohol, polyoxyethylene glycol, stearic acid and white wax and forcing the melt through an orifice. The dimensions of the obtained microspheres were particularly coarse, with an average diameter larger than a micron.

Speiser also prepared lipid microparticles (DE 3421468). In this case the preparation was based on admixing the molten lipid with a surfactant by stirring at high speed and successive ultrasound treatment.

However, no close or uniform dimensional distribution could be obtained through said process.

Summary

We have unexpectedly found that solid lipid microspheres of controlled dimensions and narrow dimensional distribution can be obtained through the process of the present invention which is characterized by:

a) contacting a molten lipid, which may contain a drug, with a mixture consisting of water, a surfactant and possibly a co-surfactant pre-heated to a temperature at least equal to the melting temperature of the lipid;

b) dispersing the obtained microemulsion in water of a temperature between 2 and 10°C;

c) washing with water through diafiltration the obtained lipid microspheres obtained in the dispersion, and lyophilizing.

As an alternative, the mixture obtained in a) is added to a mixture of water, surfactant, co-surfactant and lipids heated to a temperature at least equal to the melting temperature of said lipids, and the thus obtained mixture is dispersed in water at a temperature of 2 to 10°C.

The obtained microspheres have an average diameter smaller than one micron and in particular of between 50 and 800 nm, preferably between 100 and 400 nm, and a polydispersion comprised between 0.06 and 0.90, preferably between 0.10 and 0.70.

Detailed description of the invention

The characteristics and advantages of the lipid microspheres and of the process for their preparation according to the present invention will be further illustrated in the following detailed description.

For the preparation of said microspheres, a lipid component or a mixture of lipid components, which may contain a pharmacologically active substance, is heated to the melting point; separately an aqueous solution containing one or more surfactants and possibly one or more co-surfactants is prepared, and the resulting solution is heated to a temperature equal at least to the melting temperature of the lipid component or mixture of lipid components; this solution is admixed under mild stirring with said lipid component or mixture of lipid components, obtaining a microemulsion; the microemulsion is poured under stirring in water of 2 to 10°C, obtaining the formation of well dispersed lipid microspheres; the dispersion is washed with water by diafiltration and finally lyophilized in the presence of suitable diluents and possibly of surface active agents which favour the re-dispersion.

Alternatively, said microemulsion is added to a mixture consisting of water, surfactant, co-surfactant and lipids, heated to a temperature at least equal to the melting temperature of said lipids and the thus obtained mixture is dispersed in water of 2 to 10°C thus obtaining the formation of lipid microspheres.

The lipid components employed in the process of the present invention are selected in the group comprising: triglycerides, such as for instance trilaurin and tricapryloin, fatty acids such as decanoic-, lauric-, myristic-, palmitic and stearic acid; alcohols, such as lauryl-, myristyl-, cetyl-, stearyl alcohol.

The surfactants are selected from the group comprising: sodium cholate, sodium deoxycholate, sodium glycolate,

sodium taurocholate, sodium taurodesoxycholate, lecithin and phospholipids, Tween 20, Tween 40, Tween 80, Span 20, Span 40, Span 60, Span 80, emulsifiers such as gelatin.

The co-surfactants are selected from the group comprising: low molecular weight alcohols or glycols, such as for instance butanol, hexanol, hexandiol, propylenglycol, low molecular weight fatty acids, such as for instance butyric acid and hexanoic acid, esters of phosphoric acid and benzyl alcohol.

In the preparation of the microspheres according to the present invention the various substances are employed in the following proportions:

- the lipid components, which may contain drugs, between 5 and 30%, preferably 10 and 20% by wt. of the total;
- water, between 40 and 70%, preferably 55-65% by wt. of the total;
- surfactants 8 to 30%, preferably 12-20% by wt. of the total;
- co-surfactants 0-15%, preferably 3-7% by wt. of the total.

The volume of water for the dispersion of the microemulsion is from 10 to 200, and preferably from 50 to 100 volumes per volume of microemulsion.

The process according to the present invention presents, with respect to the prior art processes, numerous advantages, among which, for instance, a better control of the dimensions and of the dimensional distribution of the microspheres, a decidedly lower energy consumption and a considerably simplified operation.

Furthermore, the washing by diafiltration leads to the elimination of all the substances present in the dispersing aqueous phase (surfactant, co-surfactant and free drug not included in the microspheres).

Said compositions afford therefore an improved control on the action and effectiveness of the drug and minimize possible effects due to the simultaneous undesired administration of auxiliary substances such as the surfactants.

The microspheres according to the present invention have an average diameter lower than one micron, in particular comprised between 50 and 800 nm and preferably between 100 and 400 nm, and a polydispersion of between 0.06 and 0.90, preferably between 0.10 and 0.70, and may be successfully employed as vehicles for pharmacologically active substances and phytopharmaceutical substances.

To illustrate the invention the following examples are reported in which the microsphere average diameter and polydispersion were determined by means of the Malvern Zetasizer II C.

Example 1

2 g stearic acid are melted at about 65°C and 0.24 g deoxycorticosterone acetate are added obtaining hot a clear solution (solution 1).

Separately a solution of Tween 20 (2.5 ml), butanol (1 ml), sodium taurodeoxyglycolate (1.30 g) in 10 ml water is prepared which is brought to 65°C (solution 2).

Solution 1 is then poured in solution 2 obtaining a clear microemulsion at 65°C, which is then dispersed under stirring in 100 volumes water per volume of microemulsion at 2°C obtaining a lipid microsphere dispersion.

At last with water by diafiltration, mannitol is added to the dispersion, which is lyophilized.

The lipid microsphere yield on stearic acid was 96% and the deoxycorticosterone acetate contents was 4.5%.

The microspheres had an average diameter of 207 nm and the polydispersion was 0.255.

Example 2

2 g stearic acid are heated to 65°C, while separately a mixture of 10 ml water, 1.3 g sodium taurodeoxycholate, 2.0 ml Tween 20 and 0.5 ml butyric acid is prepared and heated to 65°C.

By pouring this mixture in stearic acid under stirring a microemulsion, clear at 65°C, is obtained which is then dispersed in water (100 volumes per volume microemulsion) at 2°C under stirring, to obtain a lipid microsphere dispersion.

After washing by diafiltration in water, the dispersion is lyophilized. The lipid microsphere yield on stearic acid was 96%. The average microsphere diameter was 142 nm and the polydispersion 0.239.

Example 3

A mixture of 0.6 g stearic acid and 1.4 g lauric acid is heated to 47°C. Separately, a mixture of a 1% mannitol water solution, 2.75 ml Tween 20 and 1 ml butanol is heated to 47°C.

The two mixtures are put together under stirring and a microemulsion is obtained which is then dispersed at 5°C under stirring in a 2% mannitol water solution in a ratio of 100 cc/1 cc microemulsion.

After washing with water by diafiltration, lyophilization in the presence of 1% mannitol and 0.8% sodium taurodeoxycholate is performed.

The lipid microsphere yield on the lipid components was 97%. The average microsphere diameter was 250.4 nm and the polydispersion 0.591.

Example 4

A mixture of 1.4 g palmitic acid and 0.6 g decanoic acid is heated to the melting temperature of about 50°C, while a solution of 10 ml water, 2 ml Tween 20, 1.2 g sodium taurodeoxycholate and 1 ml butanol is prepared separately and heated to 50°C.

By adding the two mixtures together, a microemulsion is obtained which is dispersed in 50 vol. water per volume of microemulsion, at 5°C under stirring obtaining a microparticle dispersion.

Washing by diafiltration with water and lyophilization follow.

The lipid microsphere yield on the lipid components was 90%, the average microsphere diameter 261 nm and the polydispersion 0.381.

Example 5

0.4 g purified egg lecithin and 0.6 g stearic acid are admixed at 64°C, and the mixture is added to a solution of 1 ml Tween 20 in 10 ml water, apart prepared and which is heated to 64°C, under stirring.

A clear microemulsion is obtained which is dispersed in water at 2°C, in a ratio of 100 vol. water per vol. of microemulsion, under stirring.

Washing with water by diafiltration and lyophilization follow.

The lipid microsphere yield on the lipid components was 87%, while the microspheres have an average diameter of 306 nm and the polydispersion is 0.667.

Example 6

2.05 g Tween 20, 2.9 g sodium taurodeoxycholate, 1.45 g butyric acid and 15.7 g water are heated to 45°C and to this mixture 2.5 g of a mixture of stearic and lauric acid (30:70), 0.05 g water and 0.25 g Span 60 heated to the same temperature is added.

The clear dispersion thus obtained is dispersed in 20 vol. water, obtaining microspheres with an average diameter of 350 nm, while the polydispersion is 0.56.

Washing by diafiltration and lyophilization follow. The yield is 91%.

Example 7

0.60 g stearic acid, 0.150 g salbutamol, 0.150 g egg lecithin, mixed together at 60°C, are added to a solution containing Tween 20 (0.63 g), butyric acid (0.4), water (3 g) kept at 60°C. A clear solution is obtained which is dispersed in cold water slightly acidified with hydrochloric acid. Lipospheres are obtained, which are washed by diafiltration and finally lyophilized.

Average diameter: 350 nm, polydispersion: 0.32.

Liposphere yield on the lipid components: 88%.

Salbutamol in the lipospheres: 4.2%

Example 8

To a mixture of water (7 g), taurodeoxycholate (0.9 g), butyric acid (0.65) heated to 45-48°C, a mixture, kept at the same temperature, of (40:60) stearic and lauric acid (1.1 g), a water solution (1.4 mg/ml) of LH-RH (0.02 ml), Span 60 (0.11 g), egg lecithin (0.11 g) was added. From the obtained clear solution, by dispersion in cold

water (1:25), lipospheres are obtained which are washed and lyophilized. Liposphere yield (on the lipid components): 85%.

LH-RH in the lipospheres: 0.015%.

Average diameter: 360 nm, polydispersion: 0.42.

Example 9

1.2 g stearic acid are added, at 60°C, to 0.160 g estradiol and 0.300 g egg lecithin, then the whole is admixed with a butanol (0.5 g) solution in 7 g water and Tween 20 (0.75 g). A clear solution is obtained which is dispersed in cold water. Lipospheres are obtained which are then washed by diafiltration and lyophilized.

Liposphere yield (on the lipid components): 75%.

Average liposphere diameter: 310 nm, polydispersion: 0.20.

Estradiol in the lipospheres: 5.2%.

Example 10

2 g stearic acid, 0.5 g naphthalene-acetic acid are admixed at 60°C and added to a mixture, kept at 60°C, of butyric acid (0.6 g), taurodeoxycholate (1.3 g), Tween 20 (2 g), water (10 g). A clear solution is obtained which is then dispersed in cold water.

After washing by diafiltration and lyophilisation, lipospheres of an average diameter of 420 nm and 0.32 polydispersion are obtained. Yield on the lipid components: 85%. Naphthalene-acetic acid in the lipospheres: 4.1%.

Example 11

A mixture consisting of 0.031 ml of a water solution (5 mg/ml) of salmon calcitonin, 1.38 g stearic acid, 0.148 g Span 40 is prepared at 65-70°C. This mixture is added to another mixture consisting of 6.85 g water, 0.84 g taurodeoxycholate, 0.59 g butanol and 8.16 g Tween 20, and kept at 65-70°C. The clear solution obtained is dispersed in cold water (1:25) and the lipospheres are washed and lyophilized. Liposphere yield, on the lipid components: 90%.

Average diameter: 300 nm, polydispersion: 0.5.

Calcitonin in the lipospheres: 0.5%.

Example 12

A mixture consisting of 0.032 ml of a water solution (2 mg/ml) somatostatin, 1.61 g palmitic/stearic acid (50:50) and 0.157 g Span 80, is prepared at 60-65°C; this mixture is then added, always at 60-65°C, to another mixture prepared with 9.675 g water, 0.75 g taurodeoxycholate, 0.57 g butyric acid, 2.13 g Tween 80, 0.075 g lecithin. The clear solution obtained is dispersed in cold water and the lipospheres are washed by diafiltration and lyophilized.

Liposphere yield, on the lipids: 88%.

Average diameter: 310 nm, polydispersion: 0.40.
Somatostathin in the lipospheres: 0.15%.

Example 13

A mixture consisting of 0.022 ml of a water solution (5 mg/ml) of erythropoietin, 1.0 g stearic/myristic acid (50:50) and 9.0 g Span 60 is prepared at 55-60°C; this mixture is then added, always at 55-60°C, to another mixture prepared from 5.535 g water, 0.495 g taurodeoxycholate, 1.35 g sodium laurylsulphate, 0.495 g butanol. The clear solution obtained is dispersed in cold water; the lipid nanospheres obtained are washed and then lyophilized, with a yield of 83% on the lipids. Erythropoietin in the lipospheres: 0.4%. Average diameter: 390 nm, polydispersion: 0.35.

Claims

1. Solid lipid microspheres having an average diameter lower than one micron and a polydispersion of between 0.06 and 0.90. 20
2. Microspheres according to claim 1, characterized by a polydispersion of between 0.10 and 0.70. 25
3. Microspheres according to claim 1, characterized by an average diameter of between 50 and 800 nm.
4. Microspheres according to claim 1, characterized by an average diameter of between 100 and 400 nm. 30
5. Microspheres according to claim 1, characterized in that the lipid substances are selected from the group comprising triglycerids, such as trilaurin and tricapryloin, fatty acids such as decanoic-, lauric-, myristic-, palmitic- and stearic acid, and alcohols such as lauryl-, myristyl-, cetyl- and stearyl alcohol. 35
6. Microspheres according to claim 1, characterized in that they contain pharmacologically active substances. 40
7. Process for preparing solid lipid microspheres with an average diameter below 1 micron and a polydispersion of between 0.06 and 0.90 and preferably between 0.10 and 0.70, characterized in that: 45
 - a) a molten lipid, which may contain a drug, is contacted with a mixture consisting of water, a surfactant and possibly a co-surfactant heated to a temperature at least equal to the melting temperature of the lipid; 50
 - b) the obtained microemulsion is dispersed in water of 2 to 10°C;
 - c) the obtained lipid microsphere dispersion is washed with water by diafiltration and lyophilized. 55
8. Process according to claim 7, characterized in that the microemulsion obtained in a) is added to a mixture consisting of water, surfactant, co-surfactant and lipids heated to a temperature at least equal to the melting temperature of said lipid substances and the thus obtained mixture is dispersed in water of 2 to 10°C. 5
9. Process according to claim 7, characterized in that said lipid substance consists of one or more components selected from the group consisting of triglycerids, such as trilaurin and tricapryloin, fatty acids such as decanoic-, lauric-, myristic-, palmitic-, stearic acid, and alcohols such as lauryl-, myristyl-, cetyl- and stearyl alcohol. 10
10. Process according to claim 7, characterized in that said surfactant comprises one or more components selected from the group consisting of sodium cholate, sodium deoxycholate, sodium glycocholate, sodium taurocholate, sodium taurodeoxycholate, lecithin and phospholipids, Tween 20, Tween 40, Tween 80, Span 20, Span 40, Span 60, Span 80 and emulsifying agents such as gelatin. 15
11. Process according to claim 7, characterized in that said co-surfactant comprises one or more components selected from the group consisting of low molecular weight alcohols and glycols, such as butanol, hexandiol, propylenglycol and hexanol, low molecular weight fatty acids such as butyric- and hexanoic acid, phosphoric acid esters and benzyl alcohol.
12. Process according to claim 7, characterized in that in step a) the lipid comprises between 5 and 30%, water between 40 and 70%, the surfactant between 8 and 30% and the co-surfactant between 0 and 15% by wt. of the total.
13. Process according to claim 7, characterized in that in stage a) the lipid comprises between 10 and 20%, the water between 12 and 20% and the co-surfactant between 3 and 7% by weight of the total.
14. The process according to claim 7, characterized in that in stage b) the quantity of water employed is of between 10 and 200 volumes per volume of said microemulsion.
15. The use of solid lipid microspheres having an average diameter below 1 micron and a polydispersion of between 0.06 and 0.90, and preferably of between 0.10 and 0.70 as vehicle for pharmacologically active and phytopharmacological substances.

Patentansprüche

1. Feste Lipid-Mikrokugeln mit einem durchschnittlichen Durchmesser von weniger als einem Mikron und einer Polydispersität zwischen 0,06 und 0,90. 5
2. Mikrokugeln gemäß Anspruch 1, **gekennzeichnet** durch eine Polydispersität zwischen 0,10 und 0,70.
3. Mikrokugeln gemäß Anspruch 1, **gekennzeichnet** durch einen durchschnittlichen Durchmesser zwischen 50 und 800 nm.
4. Mikrokugeln gemäß Anspruch 1, **gekennzeichnet** durch einen durchschnittlichen Durchmesser zwischen 100 und 400 nm. 15
5. Mikrokugeln gemäß Anspruch 1, dadurch **gekennzeichnet**, daß die Lipidsubstanz ausgewählt ist aus der Gruppe, umfassend Triglyceride, wie Trilaurin und Tricapryloin, Fettsäuren wie Decan-, Laurin-, Myristin-, Palmitin- und Stearinsäure, und Alkoholen, wie Lauryl-, Myristyl-, Cetyl- und Stearylalkohol. 20
6. Mikrokugeln gemäß Anspruch 1, dadurch **gekennzeichnet**, daß sie pharmakologisch aktive Substanzen enthalten. 25
7. Verfahren zur Herstellung von festen Lipid-Mikrokugeln mit einem durchschnittlichen Durchmesser zwischen 1 Mikron und mit einer Polydispersität zwischen 0,06 und 0,90, und vorzugsweise zwischen 0,10 und 0,70, **gekennzeichnet** durch: 30
 - a) Ein geschmolzenes Lipid, das ein Arzneimittel enthalten kann, wird mit einer Mischung, bestehend aus Wasser, einem oberflächenaktiven Mittel und möglicherweise einem co-oberflächenaktiven Mittel, die auf eine Temperatur erhitzt wurde, welche wenigstens gleich der Schmelztemperatur des Lipids ist, kontaktiert; 35
 - b) die erhaltene Mikroemulsion wird in Wasser bei 2 bis 10°C dispergiert; 40
 - c) die erhaltene Lipid-Mikrokugelndispersion wird mit Wasser durch Diafiltrieren gewaschen und lyophilisiert. 45
8. Verfahren gemäß Anspruch 7, dadurch **gekennzeichnet**, daß die in a) erhaltene Mikroemulsion zu einer Mischung gegeben wird, bestehend aus Wasser, oberflächenaktivem Mittel, co-oberflächenaktivem Mittel und Lipiden, die auf eine Temperatur erhitzt wurde, die wenigstens gleich der Schmelztemperatur der Lipidsubstanzen ist, und daß die so erhaltene Mischung in Wasser bei 2 bis 10°C dispergiert wird; 50
9. Verfahren gemäß Anspruch 7, dadurch **gekennzeichnet**, daß die Lipidsubstanz aus einer oder mehreren Verbindungen, ausgewählt aus der Gruppe bestehend aus Triglyceriden, wie Trilaurin und Tricapryloin, Fettsäuren wie Decan-, Laurin-, Myristin-, Palmitin-, Stearinsäure, und Alkoholen, wie Lauryl-, Myristyl-, Cetyl- und Stearylalkohol, bestehen. 55
10. Verfahren gemäß Anspruch 7, dadurch **gekennzeichnet**, daß das oberflächenaktive Mittel ein oder mehrere Verbindungen umfaßt, die ausgewählt sind aus der Gruppe, bestehend aus Natriumcholat, Natriumdeoxycholat, Natriumglycocholat, Natriumtaurocholat, Natriumtaurodeoxycholat, Lecithin und Phosphorlipiden, Tween 20, Tween 40, Tween 80, Span 20, Span 40, Span 60, Span 80 und emulgierenden Mitteln wie Gelatine.
11. Verfahren gemäß Anspruch 7, dadurch **gekennzeichnet**, daß das co-oberflächenaktive Mittel ein oder mehrere Verbindungen umfaßt, ausgewählt aus der Gruppe, bestehend aus niedrig-molekulargewichtigen Alkoholen und Glykolen, wie Butanol, Hexandiol, Propylenglykol und Hexanol, niedrig-molekulargewichtigen Fettsäuren, wie Butter- und Hexansäure, Phosphorsäureestern und Benzylalkohol.
12. Verfahren gemäß Anspruch 7, dadurch **gekennzeichnet**, daß in Stufe a) das Lipid zwischen 5 und 30 % umfaßt, Wasser zwischen 40 und 70 % umfaßt, das oberflächenaktive Mittel zwischen 8 und 30 % umfaßt, und das co-oberflächenaktive Mittel zwischen 0 und 15 % umfaßt, jeweils auf das Gesamtgewicht bezogen. 35
13. Verfahren gemäß Anspruch 7, dadurch **gekennzeichnet**, daß in Stufe a) das Lipid zwischen 10 und 20 %, das Wasser zwischen 12 und 20 % und das co-oberflächenaktive Mittel zwischen 3 und 7 %, jeweils auf das Gesamtgewicht bezogen, umfaßt. 40
14. Verfahren gemäß Anspruch 7, dadurch **gekennzeichnet**, daß in Stufe b) die Menge des verwendeten Wassers zwischen 10 und 200 Volumen pro Volumen der Mikroemulsion beträgt. 45
15. Verwendung von festen Lipid-Mikrokugeln mit einem durchschnittlichen Durchmesser unterhalb einem Mikron und einer Polydispersität zwischen 0,06 und 0,90, und vorzugsweise zwischen 0,10 und 0,70 als Träger für pharmakologisch aktive und phytopharmakologische Substanzen. 50

Revendications

1. Microsphères lipidiques solides ayant un diamètre moyen inférieur à 1 micron et une polydispersion entre 0,06 et 0,90.
2. Microsphères selon la revendication 1, caractérisées par une polydispersion entre 0,10 et 0,70.
3. Microsphères selon la revendication 1, caractérisées par un diamètre moyen entre 50 et 800 nm.
4. Microsphères selon la revendication 1, caractérisées par un diamètre moyen entre 100 et 400 nm.
5. Microsphères selon la revendication 1, caractérisées en ce que les substances lipidiques sont choisies dans le groupe comprenant des triglycérides, tels que la trilaurine et la tricapryloïne, des acides gras tels que l'acide décanoïque, laurique, myristique, palmitique et stéarique, et des alcools tels que l'alcool laurylique, myristylique, cétylique et stéarylique.
6. Microsphères selon la revendication 1, caractérisées en ce qu'elles contiennent des substances pharmacologiquement actives.
7. Procédé de préparation de microsphères lipidiques solides ayant un diamètre moyen en dessous de 1 micron et une polydispersion entre 0,06 et 0,90, et de préférence entre 0,10 et 0,70, caractérisé en ce que :
 - a) un lipide fondu, qui peut contenir un médicament, est porté au contact d'un mélange constitué par de l'eau un surfactif et le cas échéant un co-surfactif, chauffé à une température au moins égale à la température de fusion du lipide;
 - b) la microémulsion obtenue est dispersée dans de l'eau entre 2 et 10°C;
 - c) la dispersion de microsphères lipidiques obtenue est lavée à l'eau par diafiltration et lyophilisée.
8. Procédé selon la revendication 7, caractérisé en ce que la microémulsion obtenue dans l'étape a) est ajoutée à un mélange constitué par de l'eau, un surfactif, un cosurfactif et des lipides, chauffé à une température au moins égale à la température de fusion desdites substances lipidiques et le mélange ainsi obtenu est dispersé dans de l'eau entre 2 et 10°C.
9. Procédé selon la revendication 7, caractérisé en ce que ladite substance lipidique est constituée par un ou plusieurs composants choisis dans le groupe constitué par des triglycérides tels que la trilaurine et la tricapryloïne, des acides gras tels que l'acide décanoïque, laurique, myristique, palmitique et stéarique, et des alcools tels que l'alcool laurylique, myristylique, cétylique et stéarylique.
10. Procédé selon la revendication 7, caractérisé en ce que ledit surfactif comprend un ou plusieurs composants choisis dans le groupe constitué par le cholate de sodium, le désoxycholate de sodium, le glycolcholate de sodium, le taurocholate de sodium, le taurodésoxycholate de sodium, la lécithine et des phospholipides, le Tween 20, le Tween 40, le Tween 80, le Span 20, le Span 40, le Span 60, le Span 80 et des agents émulsifiants tels que la gélatine.
11. Procédé selon la revendication 7, caractérisé en ce que ledit cosurfactif comprend un ou plusieurs composants choisis dans le groupe constitué par les alcools et glycols à bas poids moléculaire tels que le butanol, l'hexanediol, le propylène glycol, et l'hexanol, des acides gras à bas poids moléculaire tels que l'acide butyrique et l'acide hexanoïque, des esters d'acide phosphorique et d'alcool benzylique.
12. Procédé selon la revendication 7, caractérisé en ce que dans l'étape a) le lipide représente entre 5 et 30%, l'eau entre 40 et 70%, le surfactif entre 8 et 30% et le cosurfactif entre 0 et 15% en poids du total.
13. Procédé selon la revendication 7, caractérisé en ce que dans l'étape a) le lipide représente entre 10 et 20%, l'eau entre 12 et 20% et le cosurfactif entre 3 et 7% en poids du total.
14. Procédé selon la revendication 7, caractérisé en ce que, dans l'étape b), la quantité d'eau employée est entre 10 et 200 volumes par volume de ladite microémulsion.
15. L'utilisation de microsphères lipidiques solides ayant un diamètre moyen inférieur à 1 micron et une polydispersion entre 0,06 et 0,90, et de préférence entre 0,10 et 0,70, comme véhicule de substances pharmacologiquement actives et phytopharmacologiques.